REMARKS

Claim Status

Claims 1-34, 43-45 and 47-50 are pending, of which Claims 47-50 are withdrawn by the Examiner as drawn to non-elected invention.

I. Amendments

Specification Amendment

Referring to the instant application as published, US 2007/0202103, at the Examiner's request, paragraph [0020] has been amended to indicate that it is the *target-specific portion* of the claimed compound that may, in one embodiment, be a murine monoclonal antibody BC1.

Claim Amendment

Claims 2, 3 and 45 are now cancelled.

Claim 1 is amended to recite the subject mater of Claim 3, now cancelled. Additionally, Claim 1 is amended to delete the recitation "or consists of."

Claim 8 is amended to depend on Claim 7 based on the recitation in Claim 8 as originally filed in the parent application (PCT/GB2005/000007) that Claim 8 depends on "Claim 6 or 7."

Claims 11-13 are amended to correct obvious typographical errors.

Claim 14 is amended to delete the recitation "or consists of."

Claim 15 is amended to recite that the target specific portion comprises a FAB-like molecule as an antigen binding fragment.

Claim 18 is amended to correct an obvious typographical error.

Claim 19 is amended to recite that the Fc moiety comprises the CH2 and CH3 domains of a heavy chain constant region of a human IgG_1, as disclosed in paragraphs [0042] and [0043].

Claims 20-22 and 29 are amended to delete the recitation "or consists of."

Claims 24 and 33 are amended to more particularly point out that the recited polypeptides are linked by at least one disulphide bond.

Claims 30-34 are amended to correct obvious typographical errors.

Additionally, Claim 34 is amended to make it dependent on Claim 1 and to more particularly define the invention of Claim 34.

New Claim 53 is added. New Claim 53 is drawn to the subject matter of Claim 15.

New Claims 54 to 57 are added. New Claims 54 to 57 are drawn to the preferred embodiments of the claimed invention. Support for these amendments is found throughout the specification.

New Claim 58 is added. New Claim 58 is drawn to the subject matter of Claim 1, as amended and to the subject matter recited in paragraphs [0049] and [0055].

II. Objections

Specification Objections

The Examiner objected to the specification because while in some paragraphs it disclosed that BC1 antibody is a murine antibody, in other paragraphs it disclosed that BC1 antibody was human or humanized.

Applicants disagree with the Examiner's characterization of the instant disclosure of the BC1 antibody. However, in the interests of advancing prosecution of the instant application, Applicants have amended paragraphs [0017] and [0020] to clarify that the antibody known as BC1 and obtainable from a hybridoma deposited at the European Collection of Animal Cell Cultures, Porton Down, UK (Accession No. 88042101) is a murine antibody.

Applicants believe that this amendment addresses the Examiner's objection.

Claim Objections

Claim 2 is objected to as a duplicate of Claim 3. Applicants now cancelled Claim 2.

Claim 9 is objected to due to the recitation "more at least 2-fold tighter." Applicants now amended Claim 9 to recite "at least 2-fold tighter."

Claim 33 is objected to due a typographical error in the sequence ID number. Applicants now corrected this obvious error.

Applicants believe that these amendments address the Examiner's objection.

III. Claim Rejections Under 35 U.S.C. §112 - Indefiniteness

Claims 11-13, 15, 19 and 30-33 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Claim 15

Claim 15 is rejected due to the recitation of "FAB-like molecules, such as ..." The Examiner stated that the term "FAB-like molecules" is relative in nature and that the phrase "such as" is unclear under MPEP §2173.05(d).

Applicants amended Claim 25 to recite that the target specific portion comprises a FAB-like molecule as an antigen binding fragment and to delete the recitation "such as." Applicants submit that the term "FAB-like molecules" is a term of art accepted by those of ordinary skill in the art of antibodies. Applicants submit herewith Exhibit A, which is a copy of a paper by M. Better *et al.*, "*E. Coli* Secretion of an Active Chimeric Antibody Fragment", Science, Vol. 240, (1988), pp. 1041-1043. Specifically, on page 1041, leftmost column, the authors explain that antibodies differ in their susceptibility to proteolytic cleavage, and, therefore, preparations of "Fab molecules" can be "heterologous." In other words, there can be various *molecules* (plural), all similar to Fab in that they are antigen-binding portions of antibodies obtained by proteolytic cleavage of the whole antibody molecule. Because it is cumbersome to describe all possible ways in which antibodies are proteolitycally cleaved, the term "FAB-like" is used. Because such "FAB-like" molecules are all obtained by standard laboratory technique of a proteolytic cleavage, a person of ordinary skill in the art would recognize that a person in possession of an antibody is also in possession of the "FAB-like" molecules obtainable from such an antibody. Applicants submit that the term "FAB-like molecules" used in Claim 15 encompasses all such heterologous Fab molecules, the methods of preparation of which are well known to a person of ordinary skill in the art. As such, Claim 15 is not indefinite.

Reconsideration and withdrawal of the rejection of Claim 15 are requested.

Claim 19

Claim 19 is rejected due to the recitation of the term "derived." Applicants amended Claim 19 to recite that the Fc moiety comprises the CH2 and CH3 domains of a heavy chain constant region of a human IgG_1, as disclosed in paragraphs [0042] and [0043].

Reconsideration and withdrawal of the rejection of Claim 15 are requested.

Claims 11-13 and 30-33

Claims 11-13 and 30-33 are rejected due to the recitation "**a** polypeptide of SEQ ID NO: ..." Applicants have amended Claims 11-13 and 30-33 to recite "**the** polypeptide of SEQ ID NO: ...," as suggested by the Examiner.

Reconsideration and withdrawal of the rejection of Claim 15 are requested.

IV. Claim Rejections Under 35 U.S.C. §112 - Enablement

Claims 5-6, 8-10 and 20 stand rejected under 35 U.S.C. §112, second paragraph, as not enabled. The Examiner stated that the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; and (2) reproducible from the written description. The Examiner also suggested that a suitable biological deposit, *e.g.* under the Budapest Treaty, be made.

The nature of the Examiner's rejection is not understood. Applicants note that Claims 5-6, 8-10 and 20 all recite the "BC1 antibody." As described in paragraph [0017], as amended:

> In a particularly preferred embodiment of the first aspect of the invention, the target specific portion comprises of consists of a murine BC1 antibody, or an antibody capable of competing with the binding of a BC1 antibody to oncofoetal fibronectin or a fragment or variant thereof which retains the antigen binding specificity of the parent monoclonal antibody. Production of the murine BC1 antibody is described in EP 0 344 134 B, and it is obtainable from the hybridoma deposited at the European Collection of Animal Cell Cultures, Porton Down, UK (Accession No. 88042101).

Thus, the instant specification as filed provides evidence that the murine monoclonal antibody referred to in Claims 5-6, 8-10 and 20 is available to the public because (1) it has been described in a printed publication (EP 0 344 134 B) and (2) the hybridoma lines producing this antibody have been deposited with the European Collection of Animal Cell Cultures, and are publicly accessible (Accession No. 88042101).

Furthermore, Claim 5 recites: "the monoclonal antibody having specificity for oncofoetal fibronectin is a BC1 antibody, or an antibody capable of competing with the binding of a BC1 antibody to oncofoetal fibronectin." Because the BC1's antigen is known, because the BC1

antibody itself is available to the public, and because the methods of antibody production have been known for many decades, it is merely a matter of routine experimentation for one of ordinary skill in the art to obtain an antibody defined by Claim 5 and ascertain its specificity.

As such, the instant rejection is improper and should be withdrawn. Reconsideration and withdrawal of the rejection of Claim 5-6, 8-10 and 20 are requested.

V. Claim Rejections Under 35 U.S.C. §112 – Written Description

Claims 1-29, 34 and 43-45 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner stated that the scope of the claims includes the genus of functional variants of an antibody and a genus of functional variants of the IL-12 cytokine. The Examiner stated that the recitation of "variants thereof" of a monoclonal antibody having specificity for oncofetal fibronectin does not convey a common structure or function and is not defined in the specification and fails to satisfy the written description requirement. The Examiner also stated that reciting the function of stimulating Th1 immune response in mammalian host does not distinguish a particular IL-12 "functional fragment or variant thereof" and also fails to satisfy the written description requirement. The Examiner stated that only a monoclonal antibody and "fragments thereof" (*e.g.* Fab, F(ab')2, Fv, etc.) that bind oncofetal fibronectin and "IL-12", but not the full breadth of the claims, meet the written description requirement.

Applicants respectfully disagree. Applicants first note that Claim 34 is now amended to be dependent on Claim 1. As such, the arguments presented below with respect to Claim 1 apply equally to Claims 1-29, 34 and 43-45. Applicants next note that Claim 1, as amended, now recites a genus of the target specific portions, namely - the target specific portion is capable of binding an amino acid sequence within the repeat 7 domain of fibronectin. As such, Claim 1 as amended recites that the target specific portion of the claimed compound binds to a specific antigen.

Applicants now respectfully direct the Examiner's attention at the Written Description Examination Guidelines issued by the USPTO, available at the URL www.uspto.gov/web/menu/written.pdf.

Referring to Example 13 on pages 45-46, Applicants note that a claim to *an antibody capable of binding a specific antigen* was deemed to have satisfied the written description requirement. The hypothetical specification of Example 13 did not describe the actual reduction to practice of an antibody (something the Applicants' specification does describe), it did not describe a partial or a complete structure of an antibody capable of binding the specific antigen (something the Applicants' specification does describe), and it did not describe any physical or chemical properties of the claimed antibody. The hypothetical specification of Example 13 did not disclose a correlation between the function of binding to the specific antigen and the structure of the claimed antibody and it did not even describe a method of making an antibody that binds the specific antigen (something the Applicants' specification does describe). However, the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was *conventional*. Even more importantly, *a person of ordinary skill in the art would not consider knowledge of the amino acid sequence of the variable regions critical for purposes of assessing possession of the antibody.* Thus, Example 13 reaches the conclusion that the specification satisfies the written description requirement.

Similar to Example 13 of the Examination Guidelines, Applicants' Claim 1 defines a compound that includes a monoclonal antibody, or a fragment or variant thereof, capable of binding to a specific antigen. The level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional. The derivation of functional fragments or variants of an antibody (*i.e.* amino acid variants that retain the binding function) was also conventional (ELISA and other antibody-antigen binding tests have been routine in the last several decades). Finally and perhaps most importantly, as stated in Example 13 of the Guidelines, "[a] person of skill in the art would not consider knowledge of the amino acid sequence of, *e.g.*, the variable regions critical for purposes of assessing possession of the antibody." As such, Applicants submit that the entire genus of the target specific portion of the product defined in Claim 1 is fully described in the specification.

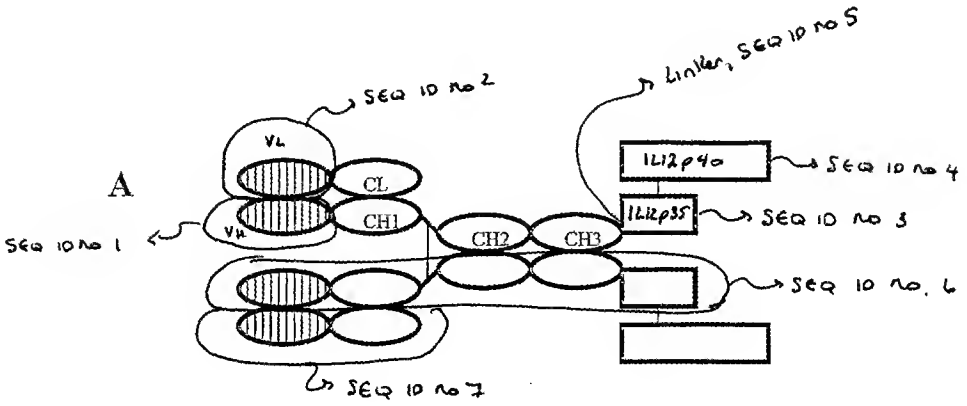
A similar argument applies to the genus of the effector portion that comprises interleukin-12, or a functional fragment or variant thereof. IL-12 is a protein known and studied extensively for decades. Its function is also well-understood (stimulation of the Th1 immune response, as

described in paragraph [0044] of the instant application as published). Thus, a test of IL-12 activity is also a matter of routine experimentation. Thus, just as "[a] person of skill in the art would not consider knowledge of the amino acid sequence of the variable regions critical for purposes of assessing possession of the antibody[,]" a person of ordinary skill in the art would not consider knowledge of the amino acid sequence of various IL-12 variants or fragments critical in assessing possession. As such, Applicants submit that the entire genus of the effector portion of the product defined in Claim 1 is fully described in the specification.

Applicants submit that Claims 54 to 57 fully satisfy the written description guidelines for the same reasons.

Additionally, Applicants now added new Claim 58 and submit that this claim is fully described under the Examination Guidelines as illustrated in Example 13 of the Written Description Examination Guidelines and further by Example 9. Example 13 has been described above. Example 9 further illustrates that a claim *to a protein that comprises a specified amino acid sequence is deemed fully described*, even where the specification does not describe other members of the genus or a complete structure. This conclusion is reached based on the existing knowledge in the art of fusion proteins, which permits one of ordinary skill to recognize that applicants were in possession of the entire claimed genus of proteins. Similarly, new Claim 56 is fully described.

To further illustrate the embodiments of Claims 1 and 54 to 58, Applicants provide the Examiner with the below reproduced drawings, which is an annotated version of FIG. 1 of the instant specification.



This drawing shows one exemplary embodiment of the present invention and does not limit the scope of the claims in any way.

Reconsideration and withdrawal of the rejections are respectfully requested.

VI. Claim Rejections Under 35 U.S.C. §103(a)

Mariani, Gilles [a] and Gilles [b]

Claims 1-7, 11-27, 34 and 43-45 are rejected under 35 U.S.C. §103(a) as being unpatentable over Mariani (Cancer, 80 (12 Suppl.):2484-2489, 1997) in view of Gilles [a] (The J. of Immunol., 160(12):6195-6203) and Gilles [b] (US 6,838,260).

The Examiner stated that Mariani teaches monoclonal antibody BC1 that binds to human oncofetal fibronectin, extremely restricted in normal adult tissues, but highly expressed in tumors. The Examiner stated that Mariani showed favorable tumor targeting *in vivo*. The Examiner is relying on Gilles [a] for its teaching of antibody-IL-12 fusion protein comprising human p35 and p40 domains. The Examiner stated that one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced BC1-IL-12, humanized BC1-IL-12 and like BC1-antigen binding fusion proteins including IL-12.

Mariani, Gilles [a], Gilles [b] and Schier

Claims 1, 5, 6, and 8-10 are rejected under 35 U.S.C. §103(a) as being unpatentable over Mariani, Gilles [a], Gilles [b] and in further view of Scheier (J. Mol. Biol., 263:551-567, 1996). In addition to the references characterized above, the Examiner is relying on Schier for its teaching of methods for producing a higher affinity antitumor antibody by restricting mutagenesis to the CDRs located at the center of the antibody combining site.

Mariani, Gilles [a], Gilles [b] and Gilles [c]

Claims 1 and 26-29 are rejected under 35 U.S.C. §103(a) as being unpatentable over Mariani, Gilles [a], Gilles [b] and in further view of Gilles [c] (WO 02/79232). In addition to the references characterized above, the Examiner is relying on Gilles [c] for its teachings of modifying amino acid residues at the junction of an antibody-cytokine fusion protein to reduce immunogenecity.

Applicants' Invention Defined in Pending Claims is Non-Obvious and Provides Unexpected Advantages

The invention defined by the pending claims, in particular Claim 1, as amended, is a compound that can be employed to target IL-12 (or its functional fragments or variants) to the neovasculature of tumors, thereby treating cancerous growth. The targeting of IL-12 to the neovasculature is improved and side effects of using IL-12 are reduced by having IL-12 fused to an antibody (or a functional fragment or variant thereof) that binds to non-ED-B regions of oncofetal fibronectin. (Claim 1, as amended, recites that "the target specific portion is capable of binding an amino acid sequence within the repeat 7 domain of fibronectin". Paragraph [0015] of the application as published explains that the repeat 7 domain of fibronectin flanks, and thus is outside, ED-B domain.)

Applicants submit that (1) one of ordinary skill in the art would *not* be motivated to target IL-12 to a non-ED-B domain; and (2) targeting IL-12 to a non-ED-B domain provides unexpected advantages.

The difference in biomedical effects of targeting within or outside of the ED-B region of oncofoetal fibronectin is dramatic. Provided herewith as Exhibit B is a copy of Courtenay-Luck and Jones, Chapter 14, "Recombinant Antibodies for Immunotherapy", Cambridge University Press (2009). Provided herewith as Exhibit C is a copy of K.-M. Lo *et al.* "HuBC1-IL12, an Immunocytokine Which Targets EDB-Containing Oncofetal Fibronectin in Tumors and Tumor Vasculature, Shows Potent Anti-Tumor Activity in Human Tumor Models", Cancer Immunol. Immunother. (2006).

As discussed in the description of the patent application, oncofetal fibronectin is a form of fibronectin that is formed in tumour cells by alternate splicing of mRNA. Oncofetal fibronectin comprises an additional domain, the ED-B domain, which is specific to oncofetal fibronectin and therefore only found in tumour cells. The ED-B domain of oncofetal fibronectin is also highly conserved and is identical in all mammals studied to date.

Therefore, the ED-B domain presents an obvious target for specifically targeting anti-cancer compounds such as IL-12, because the ED-B domain is not present in normal fibronectin. However, Applicants have instead demonstrated that antibodies which bind to a region of

oncofetal fibronectin that is outside of the ED-B region can also be used to specifically target molecules to tumor cells. The amino acid sequences of the regions of oncofetal fibronectin that are outside of the ED-B domain are identical to regions of normal fibronectin.

The skilled person would not be motivated to target areas of oncofetal fibronectin that were also found in normal fibronectin due to the strong likelihood of the normal fibronectin also bounding the targeting compound. In particular, the skilled person would not want to risk targeting IL-12 to areas outside of tumor cells because IL-12 is highly toxic (see paragraph [0003] of the specification) and it would clearly be detrimental to the health of a patient to have systemic binding of toxic molecules.

Accordingly, based on the general knowledge in this field, a skilled person would not be motivated to target a toxic molecule to a non-specific target.

Furthermore, Exhibit B, at page 193, describes the difficulty of targeting a region outside the ED-B domain using BC1 in animal models. This should be contrasted with the relative ease of using antibodies (such as L19) which recognize an epitope *within* the ED-B domain. Similarly, Exhibit C, at page 456, describes targeting huBC1 in xenograft models as not being as efficient or complete as targeting using the L19 antibody. These disclosures serve as evidence of the past and present difficulties in targeting the regions of oncofetal fibronectin outside of the ED-B domain.

Targeting the non-EB-D region, however, confers unexpected advantages. Exhibit C and Exhibit B describe, on page 452 and page 198 respectively, that the use of the non-EB-D region targeting antibody BC1 in a BC1-IL-12 conjugate exhibits reduced IL-12 bioactivity in PBMC assays as compared to the L19-IL-12 conjugate (targeting the ED-B region). The reduced stimulation of immune cells when targeting IL-12 to a non-EB-D region allows for an increased maximum tolerated dose resulting in increased effector functions. Exhibit C additionally states (page 452) that BC1 targeted IL-12 suggests a more favorable therapeutic index as well as postulating a longer serum half life and a resultant better efficacy in the clinic.

In light of all the above, one of ordinary skill in the art would not be motivated to use immunoconjugates targeting the non-ED-B regions of oncofetal fibronectin. However, such

targeting is beneficial when compared to the delivery of IL-12 to an epitope within the ED-B region. Therefore, the present invention is non-obvious.

Reconsideration and withdrawal of the rejections are respectfully requested.

VII. Claim Rejections Under Obviousness –Type Double Patenting

U.S. 7,226,998 in View of Mariani and Gilles [a]

Claims 1-7, 11-27, 34 and 43-45 are rejected on the grounds of non-statutory obviousness type double patenting as being unpatentable over Claims 1-8 of U.S. 7,226,998. In addition to the previously characterized references, the Examiner stated that Claims 1-8 of U.S. 7,226,998 are drawn to a fusion [protein] comprising an immunoglobulin (Ig) moiety linked by a peptide bond to the p35 subunit of IL-12, which is linked by a peptide bond to the p40 subunit of IL-12. The Examiner stated that although U.S. 7,226,998 does not expressly teach that the antibody be a BC1 antibody; however, Mariani and Gilles [a] teach BC1.

U.S. 6,838,260 in View of Mariani and Gilles [a]

Claims 1-7, 11-27, 34 and 43-45 are rejected on the grounds of non-statutory obviousness type double patenting as being unpatentable over Claims 1-3 and 6-8 of U.S. 6,838,260. In addition to the previously characterized references, the Examiner stated that Claims 1-3 and 6-8 of U.S. 6,838,260 are drawn to a fusion protein comprising an immunoglobulin (Ig) moiety linked by a peptide bond to the p35 subunit of IL-12, which is linked by a peptide bond to the p40 subunit of IL-12. The Examiner stated that although Claims 1-3 and 6-8 of U.S. 6,838,260 do not expressly teach that the antibody be a BC1 antibody; however, Mariani and Gilles [a] teach BC1.

U.S. 6,617,135 in View of Mariani and Gilles [a]

Claims 1-7, 11-27, 34 and 43-45 are rejected on the grounds of non-statutory obviousness type double patenting as being unpatentable over Claims 1-3, 7 and 10 of U.S. 6,617,135. In addition to the previously characterized references, the Examiner stated that Claims 1-3, 7 and 10 of U.S. 6,617,135 are drawn to a fusion protein comprising an immunoglobulin (Ig) moiety linked by a peptide bond to the p35 subunit of IL-12, which is linked by a peptide bond to the

p40 subunit of IL-12. The Examiner stated that although Claims 1-3 and 6-8 of U.S. 6,838,260 do not expressly teach that the antibody be a BC1 antibody; however, Mariani and Gilles [a] teach BC1.

In response to the Double-Patenting rejections, Applicants recapitulate their arguments presented above in the section titled "*Applicants' Invention Defined in Pending Claims is Non-Obvious and Provides Unexpected Advantages.*"

Claim 1, as amended, recites that "the target specific portion is capable of binding an amino acid sequence within the repeat 7 domain of fibronectin". Paragraph [0015] of the application as published explains that the repeat 7 domain of fibronectin flanks, and thus is outside, ED-B domain. The amino acid sequences of the regions of oncofetal fibronectin that are outside of the ED-B domain are identical to regions of normal fibronectin.

The skilled person would not be motivated to target areas of oncofetal fibronectin that were also found in normal fibronectin due to the strong likelihood of the normal fibronectin also bounding the targeting compound. In particular, the skilled person would not want to risk targeting IL-12 to areas outside of tumor cells because IL-12 is highly toxic (see paragraph [0003] of the specification) and it would clearly be detrimental to the health of a patient to have systemic binding of toxic molecules.

However, targeting the non-EB-D region confers unexpected advantages. Exhibit C and Exhibit B describe, on page 452 and page 198 respectively, that the use of the non-EB-D region targeting antibody BC1 in a BC1-IL-12 conjugate exhibits reduced IL-12 bioactivity in PBMC assays as compared to the L19-IL-12 conjugate (targeting the ED-B region). The reduced stimulation of immune cells when targeting IL-12 to a non-EB-D region allows for an increased maximum tolerated dose resulting in increased effector functions. Exhibit C additionally states (page 452) that BC1 targeted IL-12 suggests a more favorable therapeutic index as well as postulating a longer serum half life and a resultant better efficacy in the clinic.

Applicants submit that nothing in the cited claims of the U.S. 7,226,998, U.S. 6,838,260 or U.S. 6,617,135 or in the disclosure of the cited references motivates or suggests to one of ordinary skill in the art to target IL-12 to a non-ED-B domain and that targeting IL-12 to a non-ED-B domain provides unexpected advantages. In light of all the above, one of ordinary skill in

the art would not be motivated to use immunoconjugates targeting the non-ED-B regions of oncofetal fibronectin. However, such targeting is beneficial when compared to the delivery of IL-12 to an epitope within the ED-B region. Therefore, the present invention is non-obvious.

Reconsideration and withdrawal of the rejections are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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Concord, MA 01742-9133
Date: February 18, 2010